REMARKS

Solely to expedite prosecution, Claims 1, 2, 4-15, 18, 19, and 21-32 have been canceled without prejudice to pursuing these claims in a divisional or continuing application. Applicants do not hereby abandon or waive any rights in the subject matter of canceled Claims 1, 2, 4-15, 18, 19, and 21-32. Applicants reserve the right to pursue the canceled subject matter in a divisional or continuing application.

No new matter has been added by the amendments. Therefore, entry of this Amendment into the present application is respectfully requested.

Rejection of Claims 1, 2, 4-15, 18, 19 and 21-32 Under 35 U.S.C. § 112, Second Paragraph

The rejection of Claims 1, 7, 18, and 24 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, was maintained for reasons of record. Applicants will address the Examiner's rejections of the particular claims in the order that they were presented by the Examiner.

The Examiner maintains that Claims 1 and 18, which recite an epitope specific for human TNF alpha, are rejected as vague and indefinite because, according to the Examiner, it is unclear if the specificity is to be evaluated in relation to TNF alpha of other species such as rabbit or mouse, or if the specificity is to be evaluated in relation to human TNF-beta or gamma.

For the purpose of maintaining the record, Applicants reiterate their previously submitted arguments as set forth in the Amendment filed on January 21, 2003. A claim and its limitations are interpreted in light of the teachings of the Specification. Applicants clearly teach that the claimed antibodies are specific for human TNF-α when evaluated in relation to TNF-α of other species (*i.e.*, rabbit or mouse) **and** when evaluated in relation to human TNF-beta or gamma. (See, for example, the instant specification at Example X at page 81, line 13 to page 82, line 10). Thus, Claims 1 and 18 are definite.

As indicated above, Claims 1 and 18 have been canceled herein. While Applicants do not agree with the rejection, the claims were canceled in order to expedite prosecution of the application. In view of the claim cancellations, the rejection is obviated.

The Examiner maintains that Claims 7 and 24, which recite " high affinity", are rejected because, according to the Examiner, the term "high affinity" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree.

For the purpose of maintaining the record, Applicants reiterate their previously submitted arguments as set forth in the Amendment filed on January 21, 2003. The term "high affinity" is a standard term used by one of skill in the art to describe an antibody's affinity for its ligand regardless of its ability to block the activity of TNF-α, *in vitro*. An antibody can bind to its ligand with high affinity and, yet, have no effect on the activity of the ligand. The **general** use of the term "high affinity" is evidenced by Möller *et al.* (*Cytokine*, v.2(3): 162-169 (1990), cited by the Examiner in the below 35 U.S.C. §103(a) rejection) at page 165, col. 2, lines 22-25, where Möller *et al.* use the phrase "high affinity monoclonal antibodies". The only support relied upon in Möller *et al* for this phrase is the affinity constants for the antibodies as shown in Table 1 of Möller *et al.* One of skill in the art would understand, based on an antibody's binding affinity for its ligand, whether the antibody bound to its ligand with low, moderate or high affinity. Thus, Claims 7 and 24 are definite and distinctly claim that which Applicants regard as the invention.

As indicated above, Claims 7 and 24 have been canceled herein. While Applicants do not agree with the rejection, the claims were canceled in order to expedite prosecution of the application. In view of the claim cancellations, the rejection is obviated.

It is noted that the rejection to Claim 17 on this ground has been withdrawn.

Rejection of Claims 11-13 and 28-30 Under 35 U.S.C. § 112, First Paragraph

The rejection of Claims 11-13 and 28-30 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is maintained for reasons of record. Specifically, in the previous Office Action the Examiner stated that:

> The specification sets forth on page 72 and figure 3 the results of an in vitro cytotoxicity assay with the cA2 antibody. It is noted that in figure 3 the concentration of the antibody is given in ng/ml. Claims 11-13, 28-30 and 52-54 are drawn to ID50s on the order of ug/ml and ng/ml. Given the inconsistencies within the

> specification, one of skill in the art would not know how to make or use the claimed antibodies having the recited ID50 values, because one of skill in the art would not be able to ascertain the actual ID50 of the cA2 antibody. Therefore, one of skill in the art would be subject to undue experimentation in order to make and use the claimed antibodies having specific ID50 values.

For the purpose of maintaining the record, Applicants reiterate their previously submitted arguments as set forth in the Amendment filed on January 21, 2003. In Figure 3, the concentration of the antibody is given in ng/ml. However, Applicants draw the Examiner's attention to the 1000 ng/ml concentration point shown in Figure 3. 1000 ng/ml is the same as 1 μg/ml because 1 ng equals 10^{-3} μg. Therefore, there are no inconsistencies within the specification. One of skill in the art would know how to make and use the claimed antibodies having the recited ID50 values, because one of skill in the art would be able to convert ng/ml to μg/ml, and vice-versa, without undue experimentation and, thus, ascertain the actual ID50 of the cA2 antibody. Moreover, Applicants teach methods which can be used to determine TNF neutralizing activity of a TNF neutralizing compound, and teach the ID50 values obtained for the claimed antibodies. (See the Detailed Description at page 53, lines 23-27, and Examples II and XI).

As indicated above, Claims 11-13 and 28-30 have been canceled herein. While Applicants do not agree with the rejection, the claims were canceled in order to expedite prosecution of the application. In view of the claim cancellations, the rejection is obviated.

It is noted that the rejection to Claims 52-54 on this ground has been withdrawn.

Rejection of Claims 1, 2, 4-10, 14, 15, 18-27, 31 and 32 under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4-10, 14, 15, 18-27, 31 and 32 are rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner:

> the specification, while being enabling for chimeric antibodies containing all of the variable regions of the parent non-human antibody, said chimeric antibody having unspecified binding affinity for TNF alpha does not reasonably provide enablement for antibodies or polypeptides which compete with cA2 for binding to hTNF, chimeric antibodies which are not cA2 having Ka values of at least 1 x 10^8 L/mole or 1 x 10^9 L/mole, or fragments of antibodies or polypeptides, thereof.

For convenience, the remainder of this rejection will be addressed under the appropriate subheadings as outlined by the Examiner.

A) Rejection of Claims 8-10 and 25-27 as drawn to chimeric antibodies other than cA2 which compete for binding with cA2 and have affinity constants of 1×10^8 or 1×10^9.

The Examiner maintains that, given the teachings of the specification regarding the unexpected high binding affinity of the cA2 antibody, the teachings of Mateo (Mateo *et al.*, *Hybridoma*, v.19, pp. 463-471 (2000)) regarding the expectation of lower binding affinity for a chimeric antibody, and the teachings of Adair (Adair *et al.*, WO 92/11383) regarding the necessity of altering framework regions to improve binding affinity, it can be concluded that the specification is lacking in teachings on how to make other chimeric antibodies which bind to TNF-α with the claimed affinity constants or having the ability to competitively inhibit the binding of cA2 to TNF-α. Thus, according to the Examiner, given the lack of teachings and the unpredictability of the art as exemplified by Mateo and Adair, a person of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make chimeric antibodies other than cA2 which would have these claimed elements.

For the purpose of maintaining the record, Applicants reiterate their previously submitted arguments as set forth in the Amendment filed on January 21, 2003. Applicants direct the Examiner's attention to the Federal Circuit decision in *In re Wands,* 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (a copy of which was submitted as Exhibit D along with the Amendment dated January 21, 2003). The claims at issue in *Wands* recited methods for immunoassay of HbsAg using high affinity monoclonal antibodies that the Appellants found to have unexpectedly high sensitivity and specificity. The position of the PTO was that the data presented by Appellants showed that the production of high-affinity IgM anti-HBsAG antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

As stated by the court in *In re Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening." The court recognized that the nature of monoclonal antibody technology is such that it involves screening hybridomas to determine which ones secrete antibodies with desired characteristics, and that practitioners of this art are

prepared to screen negative hybridomas in order to find one that makes the desired antibody. The court went on to state that "in the monoclonal art it appears that experimentation is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen."

Applicants maintain their position that the written Specification fully enables the practice of the claimed invention because the claimed antibodies can be made from readily available starting materials using methods that are well known in the art. For example, it teaches a method of producing the claimed chimeric antibodies according to the present invention (See instant Detailed Description at page 32, lines 7 through 24 and Examples III-IX). Additionally, it teaches methods of cloning a polynucleotide encoding an anti-TNF variable or constant region. (See, for example, instant Detailed Description at page 28, line 8 through page 30, line 4 and page 30, line 5 through page 31, line 2). Furthermore, the instant specification teaches that preferred anti-TNF mAbs also include those which will competitively inhibit *in vivo* the binding to human TNF-α of anti-TNF-α murine mAb A2, chimeric mAb cA2, or an antibody having substantially the same specific binding characteristics, as well as fragments and regions thereof. (See instant Detailed Description at page 19, line 25 through page 20, line 2). It also teaches preferred methods for determining mAb specificity and affinity (See, for example, instant Specification at Examples X and XI). Thus, a person of skill in the art would not be subject to undue experimentation without reasonable expectation of success in order to make chimeric antibodies other than cA2 which would have these claimed elements.

Furthermore, MPEP §2164.08 states that all questions of enablement are evaluated against the claimed subject matter. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Thus, the determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The second is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 169 USPQ 236,

239 (CCPA 1971). Therefore, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, *e.g.*, *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Claims 9, 10, 26 and 27 recite chimeric antibodies comprising part of a human immunoglobulin constant domain and part of a non-human variable region, said antibodies binding to TNF-α with affinity constants of at least 1×10^8 or 1×10^9. Additionally, Claims 8 and 25 recite chimeric antibodies which competitively inhibit the binding of cA2 to TNF-α. The scope of enablement disclosed in the instant application must only bear a "reasonable correlation" to these claimed chimeric antibodies. As long as the Specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

As discussed above, the instant Specification provides ample teachings such that one of skill in the art would not be subject to undue experimentation in order to make or use the claimed antibodies. Thus, the skilled artisan is enabled to use the claimed invention commensurate in scope with the claims, thereby, meeting the requirements established by *In re Fisher*.

As indicated above, Claims 8-10 and 25-27 have been canceled herein. While Applicants do not agree with the rejection, the claims were canceled in order to expedite prosecution of the application. In view of the claim cancellations, the rejection is obviated.

(B) Rejection of Claims 1, 2, 4-10, 14, 15, 18, 19, 21-27, 31 and 32 as encompassing chimeric antibodies containing less than all of the light and heavy chain variable regions of parent non-human antibody.

The Examiner maintains the rejection of Claims 1, 2, 4-10, 14, 15, 18, 19, 21-27, 31 and 32. According to the Examiner, it is "well established" in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody; therefore, the Examiner relies on Paul (Paul, *Fundamental Immunology*, 3rd Ed., page 292-293 (1993)) to state that it cannot be expected that antibodies or polypeptide comprising less than the full variable regions of SEQ ID NO: 3 or SEQ ID NO: 5 will form the identical ligand binding surface. Thus, according to the Examiner, it is unlikely that antibodies, polypeptides or fusion proteins as defined by the claims which contain less than

the full heavy or light chain variable regions of the cA2 antibody and fused to any human framework sequence or comprised of any polypeptide sequence would have the required binding function. Therefore, the Examiner states that the specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims and undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

For the purpose of maintaining the record, Applicants reiterate their previously submitted arguments as set forth in the Amendment filed on January 21, 2003. Paul describes the general structure of an antibody and states that the vast sequence possibilities in the variable domain, and the unique folding of variable region polypeptides, result in the diverse repertoire of antibody binding specificities. The teachings of Paul do not support the statements made by the Examiner regarding Paul's applicability to the instant claims. Applicants are not claiming that antibodies or polypeptides comprising less than the full variable regions of SEQ ID NO: 3 or SEQ ID NO: 5 will form an identical ligand binding surface as antibodies or polypeptides comprising SEQ ID NO: 3 or SEQ ID NO: 5. Rather, Applicants are claiming chimeric antibodies, polypeptides, or a fusion protein, comprising all or part of the light and heavy chain variable regions of a parent non-human antibody and polypeptide fragments of SEQ ID NO: 3 and/or SEQ ID NO: 5 which competitively inhibit the binding of cA2 to TNF-α. Moreover, Applicants have provided ample support to cover the scope of the instant claims.

The only relevant concern regarding the scope of enablement provided to one skilled in the art by the disclosure is whether the scope of enablement is commensurate with the scope of protection sought by the claims. *In re Moore*, 169 USPQ 236, 239 (CCPA 1971). Thus, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

In the instant application, the scope of enablement disclosed in the instant application must only bear a "reasonable correlation" to chimeric antibodies comprising part of SEQ ID NO: 3 and part of SEQ ID NO: 5, polypeptides comprising either SEQ ID NO: 3 or SEQ ID NO: 5, polypeptides comprising fragments of either SEQ ID NO: 3 or SEQ ID NO: 5, fusion proteins comprising SEQ ID NO: 3 or SEQ ID NO: 5 and fragments of said fusion proteins. As long as the Specification discloses at least one method for making and using the claimed invention that

bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1978).

As stated above, Applicants provide ample guidance within the specification (which is over 160 pages long) and figures to enable the rejected claims. Claims 1, 2, 4-10, 14, 15, 18, 19, 21-27, 31 and 32 encompass chimeric antibodies comprising all or part of the light and heavy chain variable regions of a parent non-human antibody.

The Specification teaches a method of producing a chimeric antibody according to the present invention (See the Detailed Description at page 32, lines 7 through 24). The Specification also teaches that preferred anti-TNF mAbs, as well as fragments and regions thereof, are those which will competitively inhibit *in vivo* the binding to human TNF-α of anti-TNF-α murine mAb A2, chimeric mAb cA2, or an antibody having substantially the same specific binding characteristics. (See the Detailed Description at page 19, line 25 through page 20, line 2). Applicants' Specification also teaches preferred methods for determining mAb specificity and affinity by competitive inhibition (See, for example, Specification at Examples X and XI). Contrary to the Examiner's assertion, the Specification teaches methods of cloning a polynucleotide capable of expressing a protein which competitively inhibits the binding of an anti-TNF antibody, such as A2 or cA2, and which has a nucleotide sequence that is capable of encoding polypeptides that have the same amino acid sequence as anti-TNF antibodies or fragments thereof. (See, for example, instant Detailed Description at page 28, line 8 through page 31, line 2).

Applicants' Specification teaches one skilled in the art how the claimed antibodies were prepared and how the claimed antibodies were tested for their functional properties. Therefore, the disclosure bears a reasonable correlation to the entire scope of the claims and enables one of skill in the art to make and use the claimed invention.

As indicated above, Claims 1, 2, 4-10, 14, 15 , 18, 19, 21-27, 31 and 32 have been canceled herein. While Applicants do not agree with the rejection, the claims were canceled in order to expedite prosecution of the application. In view of the claim cancellations, the rejection is obviated.

It is noted that the rejection to Claims 37, 40-42 and 48-51 on these grounds has been withdrawn.

Rejection of Claims 1, 2, 4-7, 15, 18, 19, 21-24, and 32 Under 35 U.S.C. § 103(a)

The rejection of Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 under 35 U.S.C. §103(a) as being unpatentable over Möller *et al.* (*Cytokine*, v.2, pp.162-169 (1990))("Möller") in view of Zerler (EP 380,068) as evidenced by Morrison *et al.* (In: Antibody Engineering, Ed. Borrebaeck, p. 291 (1995))("Morrison") is maintained for reasons of record. The Examiner maintains that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a chimeric antibody having a IgG1 constant region, wherein the variable region was derived from murine mAb195 antibody of Möller.

For the purpose of maintaining the record, Applicants reiterate their previously submitted arguments as set forth in the Amendment filed on January 21, 2003. Applicants' invention is drawn to chimeric antibodies which bind an epitope specific for human TNFα. In contrast, the antibodies of Möller *et al.* are not chimeric, rather they are mouse monoclonal antibodies. One of the main problems associated with the use of murine antibodies in pharmaceutical treatments in humans was the possibility that a harmful immunological Human Anti-Mouse Antibody (HAMA) response, can occur once the murine is administered to a human. Applicants were the first to successfully incorporate human sequence into a neutralizing murine antibody for TNFα, to reduce the immunological effect while still maintaining the high binding affinity and pharmaceutical effectiveness of the parent antibody. Möller *et al.* fail to report a HAMA response or suggest the manufacture or use of a chimerized antibody to prevent the response in clinical treatment, or that chimerizing the disclosed antibody would sufficiently reduce the HAMA response to be therapeutically advantageous. Thus, one of skill in the art would not be motivated, and would be without a reasonable expectation of success, to modify the teachings of Möller *et al.* to obtain the claimed chimeric antibodies.

Furthermore, Möller *et al.* do not describe antibodies which possess the characteristics of Applicants' claimed chimeric antibodies. For example, Möller *et al.* teaches that monoclonal antibody mAb 114 shows cross-reactivity with TNF-α of cynomolgus, rhesus and baboon; mAb 199 does not neutralize the cytotoxicity of human TNF-α. In fact, the Möller *et al.* reference does not describe the *in vivo* neutralizing ability of any antibody described for use in the treatment of humans. The *in vitro* studies taught in Möller *et al.* were limited to determining the

ability of their anti-TNF antibodies to bind to TNF and to alter some features of its biological activity. However, these *in vitro* studies do not suggest the clinical protocols or results of effective administration of anti-TNF antibodies in humans. They do not establish that anti-TNF antibody administration would have any effect on TNF-mediated disease *in vivo*, or the magnitude and duration of the clinical response and possible adverse reactions of that therapy. TNFα is known to contain many epitopes. A skilled artisan, on the basis of the information disclosed in these references, would not conclude that any of the prior art antibodies are identical to or contain the features of the antibodies claimed by Applicants.

To maintain a rejection based on obviousness, it must be demonstrated that at the time of the invention, one of skill in the art would have been motivated to chimerize the murine antibodies taught by Möller *et al.* to produce Applicants' claimed compounds with a reasonable expectation of success. See *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991). Zerler *et al.* fails to provide this necessary motivation.

As discussed above, the Möller *et al.* reference does not provide the teachings for producing TNF neutralizing antibodies that can be used for *in vivo* diagnostic or therapeutic uses in humans. By contrast, Applicants' claimed antibodies have been demonstrated to be capable of neutralizing TNFα in a clinical setting with superior results. Furthermore, Zerler *et al.* does not provide that which Möller *et al.* reference lacks. Zerler *et al.* does not teach TNF neutralizing antibodies. Rather, it is the object of Zerler *et al.* to provide a generic expression system for producing chimeric antibodies that allows for insertion of a non-human variable region without mutagenesis of the variable region.

As noted by the Examiner, Zerler *et al.* does not teach that the recombinant chimeric antibody from the disclosed method would contain two light chains and two heavy chains. The Examiner relies on the teaching by Morrison *et al.* (at page 291), to provide this support. According to the Examiner, Morrison *et al.* teaches that transfectomas generally secrete IgGs as H2L2 (two heavy chains and two light chains). However, this is irrelevant since one of skill in the art would not have been motivated to chimerize the murine antibody taught by Möller *et al.* to produce Applicants' claimed compounds with a reasonable expectations of success based upon the teachings of Zerler *et al.*

Thus, the combination of references do not teach or suggest the preparation of chimeric antibodies which bind TNFα, do not provide a reasonable expectation of achieving a chimeric antibody of reduced immunogenicity and/or possessing a therapeutic benefit *in vivo* and do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. As such, the claimed invention is not obvious over the cited references.

As indicated above, Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 have been canceled herein. While Applicants do not agree with the rejection, the claims were canceled in order to expedite prosecution of the application. In view of the claim cancellations, the rejection is obviated.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Registration No. 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
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